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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/369,236	08/04/1999	GRANT A. KRAFFT	97002-C	6514

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EXAMINER	
GUPTA, ANISH	
ART UNIT	PAPER NUMBER
1653	9

DATE MAILED: 06/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/369,236	KRAFFT ET AL.	
	Examiner	Art Unit	
	Anish Gupta	1653	

-- The MAILING DATE of this communication appears on the cover sh et with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *15-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restriction

1. Applicant's election of Group I, claims 1-14, in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 15-44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group II-XVI, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to amyloid beta assemblies wherein assembly comprises 3 to 12 amyloid beta proteins. However, it is unclear which amyloid beta proteins the claims are making reference to. It is known in the art that various amyloid beta proteins with varying lengths are known in the art. For example, the art has recognized that amyloid beta 1-39, 1-40, 1-40 and 1-43. However it is unclear from the claim which amyloid beta protein the claims are making reference and therefore the claim is rendered indefinite.

3. Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for amyloid β (1-42), does not reasonably provide enablement for any amyloid β protein to form a non-fibrillar product. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to enable the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention is drawn to amyloid beta assemblies having 3 to 12 amyloid beta proteins that are non-fibrillar.

(2) The state of the prior art

The art teaches that amyloid beta proteins form fibrils. For example, Burdick et al. teach that amyloid beta protein 1-28 formed amyloid like fibrils (see abstract). Halverson et al. teach that the sequence 34-42, by virtue of its ability to form unusually stable beta-structure, is a major

contributor to the formation of the fibrils that constitute amyloid plaque (see abstract). The reference further states that peptide β34-42 exists exclusively as a beta-sheet which will not desegregate in water (see page 2643). Even in organic solvents, β34-42 failed to dissolve and thus reflected the reluctance of this sequence to form a soluble helix or coil. The reference concludes that strong intermolecular interactions between a sequence comprising at least nine amino acids at the C-terminus of the β-protein results in self association and formation of antiparallel cross-β fibrillar core (see page 2643). Moreover, reference of Kuo et al. imply that "the incorporation of wsAβ N-42 into insoluble filaments occurs only after it has oligomerized into ocatameric and larger molecules." (See page 4080). Thus the Kuo et al. reference leads on to believe that structures larger than octamers cannot form non-fibrillar structures.

(3) The relative skill of those in the art

The relative skill of the those in the art is high.

(4) The predictability or unpredictability of the art

Since the art indicates that amyloid beta proteins are fibrillar and intermolecular interactions between a sequence comprising at least nine amino acids at the C-terminus of the β-protein results in self association and formation of antiparallel cross-β fibrillar core, one would expect an amyloid beta protein assembly to be fibrillar. Therefore, predictability of an amyloid beta protein assembly to be non-fibrillar would be highly unpredictable.

(5) The breadth of the claims

The claims are open to any amyloid beta protein. In the broadest breath of the claims, the claims are also inclusive of amyloid beta fragments, such as β34-42.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples

The specification, provides guidance as to the assembly of the amyloid beta structures through self association and exogenous cross linking agents. The specification provides guidance of the amyloid beta assemblies exhibiting neurotoxic activity. However, the specification fails to provide ample guidance that the product obtained is non-fibrillar. Moreover, the specification fails to provide guidance that any amyloid beta protein or its fragments would result in assemblies that are non-fibrillar. The working examples provide guidance as to the preparation of the amyloid β oligomer but does not clearly demonstrate that the method resulted in a non-fibrillar complex. As state above, the art has indicated that amyloid beta proteins are fibrillar including both β 1-28. Moreover, the art also teaches that strong intermolecular interactions between a sequence comprising at least nine amino acids at the C-terminus of the β-protein results in self association and formation of antiparallel cross-β fibrillar core. Therefore, one would conclude that the amyloid beta assemblies comprising amyloid beta protein 1-28 would result in the assemblies that are fibrils. Further, this is also true of structures greater than octamers. The specification and the working examples have not disclosed any examples that would contradict the findings and the conclusions established by the Kuo reference. Without clear demonstration, one would not be able to ascertain if any amyloid beta protein would result in non-fibrillar assemblies.

(8) The quantity of experimentation necessary

Due to the teaching in the art, specifically that amyloid beta protein form fibril structures and that the C-terminal sequence plays a pivotal role in the formation of fibril structures, one of ordinary skill in the art could not reasonably predict if the assemblies of the instant application are non-fibrillar.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-2, 4, 6, 7-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Levine.

The claims are drawn to a non fibrillar amyloid β proteins.

The reference of Levine et al. teach the formation of hexameric complexes of preamyloid complexes in plasma and CSF (see page 758). The reference teaches that formation of the hexameric complexes is a property of the interacting peptides and is not likely to be a result of the chemistry of the cross-linking reagent (see page 760, col. 2). The multimers, such as hexamers, associated into larger structures having a molecular weight of ~26,000 (see page 758, col. 2). The reference teaches that the multimers, from the chromatographic profile, represent prefribil species of associated β(1-40) peptide (see page 758, col. 2).

5. Claims 1-2, 7, 11, 13-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Roher et al.

The claims are drawn to non fibrillar amyloid β proteins.

The reference of Roher et al. teach trimeric forms of amyloid-β (-42). The reference states that the trimeric forms were soluble (see abstract). The reference state that the dimeric structures isolated in conjunction with the trimers were non-fibrillar (see page 20634). Thus one could conclude that the trimers would also be non-fibrillar, especially in light of the fact that the structures were soluble. The reference also states that the molecular weight of the trimers was determined to be 13.5 kda by SDS-polyacrylamide gel Tris-tricine (see abstract and 20632). Finally, the reference teaches that the diameter of the filaments was 7-8nm for the oligomeric structures (see page 20633). Thus, the reference anticipates the claimed invention.

6. Claims 1-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Kuo et al.

The claims are drawn to non fibrillar amyloid β proteins.

The reference of Kuo et al. teach oligomeric forms of amyloid-β (1-42). The reference teaches oligomeric forms of amyloid β that have a molecular weight between 10kDa and 100kDa (see abstract). The reference states the incorporation of wsAβ N-42 into insoluble filaments occurs only after it has oligomerized into ocatameric and larger molecules." (See page 4080). Therefore, the oligomeric structures less than an octamers would be in the form of non-fibrillar soluble forms. Although the reference does not teach the specific molecular weight and size of the structures, since the reference teaches up to octameric structures, oligomeric structures with the specific

molecular weight and diameter size would necessarily be isolated. Therefore, the reference anticipates the claims.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,218,506. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons.

The US Patent claims a isolated, soluble, non-fibrillar amyloid β (1-42) oligomeric structure having between 3-12 amyloid β proteins (see claim 1). The US Patent discloses structures that have

molecular weight between 23 and 24kDa and 27 and 28 kDa and having dimensions between 4.9nm 5.3 nm or 5.7nm to 6.2nm (see claim 4-7). Note that these dimensions encompass those claimed in claim 7-12 of the instant application. The difference between the US patent and the instant application is that the US Patent does not disclose the specific molecular weight claimed. However, since the US Patent discloses oligomeric structures between 3-12 amyloid β proteins, these structures would necessarily have the claimed molecular weight. Therefore, the claims of the US Patent and the instant claims overlap sufficiently to render one another as not patentably distinct from each other.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (703) 308-4001. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can normally be reached on (703)308-2923. The fax phone number of this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
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6/21/02

Anish Gupta